



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: )  
Isao WADA et al. )  
 ) Group Art Unit: 1624  
Application No. 10/574,278 )  
 ) Examiner: Berch, Mark L  
Filed: March 31, 2006 )  
 ) Confirmation No.: 7468  
For: PENICILLIN CRYSTALS AND )  
PROCESS FOR PRODUCING THE )  
SAME )  
 )

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. § 1.132

I, Isao WADA, do hereby make the following declaration:

1. I am a Japanese citizen, residing at c/o OTSUKA  
CHEMICAL CO., LTD., 463, Kagasuno Kawauchi-cho, Tokushima-shi,  
Tokushima 7710193, Japan.
2. I graduated from Kyoto Institute of Technology,  
Faculty of Engineering, Department of Synthetic Organic  
Chemistry in 1986. I also graduated from the Graduate School of  
Kyoto Institute of Technology, and received a Master's Degree in  
Engineering Research in 1988.
3. I began my employment with OTSUKA CHEMICAL CO., LTD.,  
the assignee of the above-identified application, in 1988.  
Since 1988, I have been engaged in the research and

technological development of API (active pharmaceutical ingredients) and pharmaceutical intermediates.

4. I am one of the named inventors of the above-identified application, and am familiar with the subject matter of said application as well as the disclosures in the cited references.

5. In order to confirm that the compound obtained by the recrystallization disclosed in Bull. Chem. Soc. Jpn., 62, 3046-3048 (1989) is not 2 $\beta$ -chloromethyl-2 $\alpha$ -methylpenam-3 $\alpha$ -carboxylic acid benzhydryl ester, the following experiment was conducted.

#### Experiment 1

4-Dithioazetidinone (2C) (37.5 mmol) was dissolved in dichloromethane (150 mL), 22 wt% hydrochloric acid (150 mL) was added to the resulting solution dropwise, and the mixture was then cooled. After cooling, a sodium nitrite aqueous solution obtained by adding 2.85 g of sodium nitrite to 37.5 mL of water was added dropwise to the reaction solution. The resulting reaction solution was then stirred, and aged at 0°C for 2 hours, obtaining crystals (hereunder, these crystals are referred to as "Crystal A"). Crystal A was washed with a small amount of dichloromethane to isolate Crystal A. Water, and the washing liquid used for the above-mentioned washing with dichloromethane were added to the filtrate after the isolation of Crystal A,

followed by liquid separation extraction to separate the liquid into an organic layer and a water layer. A sodium bicarbonate solution was added to the thus-obtained organic layer to conduct further liquid separation extraction to obtain an organic layer and a water layer. To the organic layer obtained by the liquid separation extraction using a sodium bicarbonate solution, brine was added to conduct further liquid separation extraction, separating the liquid into an organic layer and a water layer. To the organic layer obtained by the liquid separation extraction using brine, sodium sulfate was added and dried. Subsequently, magnesium sulfate was filtered out, and the filtrate was divided into "Filtrate 1 and "Filtrate 2". Filtrate 1 was concentrated, and a small amount of acetone was added to the resulting residue to deposit crystals. The crystals (hereunder, these crystals are referred to as "Crystal B") were separated out by filtration. The separated filtrate was concentrated, and diethyl ether was added thereto, followed by aging for 12 hours. As a result, the deposition of crystals was not observed. Filtrate 2 was also concentrated, and a small amount of methanol was added to the resulting residue to deposit crystals. The thus-obtained crystals (hereunder, referred to as "Crystal C") were isolated by filtration. The separated filtrate was concentrated, and diethyl ether was added thereto, followed by

stirring and aging for 12 hours. As a result, the deposition of crystals was not observed (oil out).

Crystal A, Crystal B, and Crystal C obtained in the above-explained process were subjected to NMR analysis (AVANCE500, manufactured by Bruker). The resulting NMR charts are shown in Figs. 1 to 3.

Fig. 1 (Crystal A)

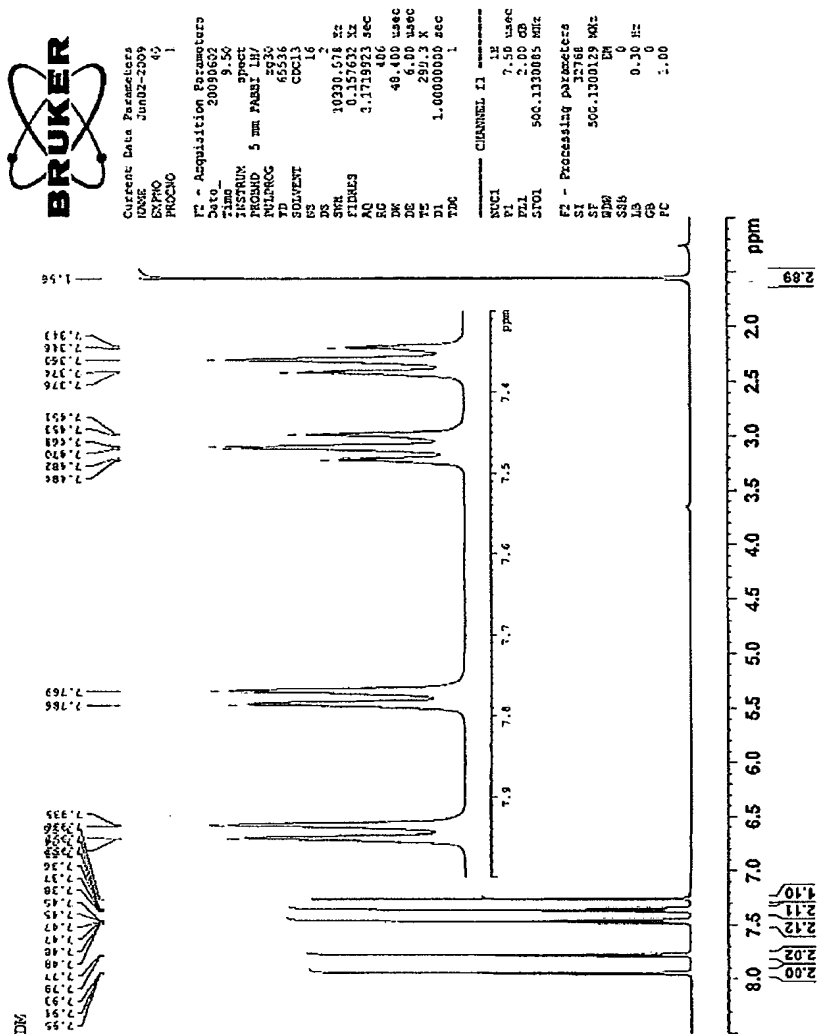
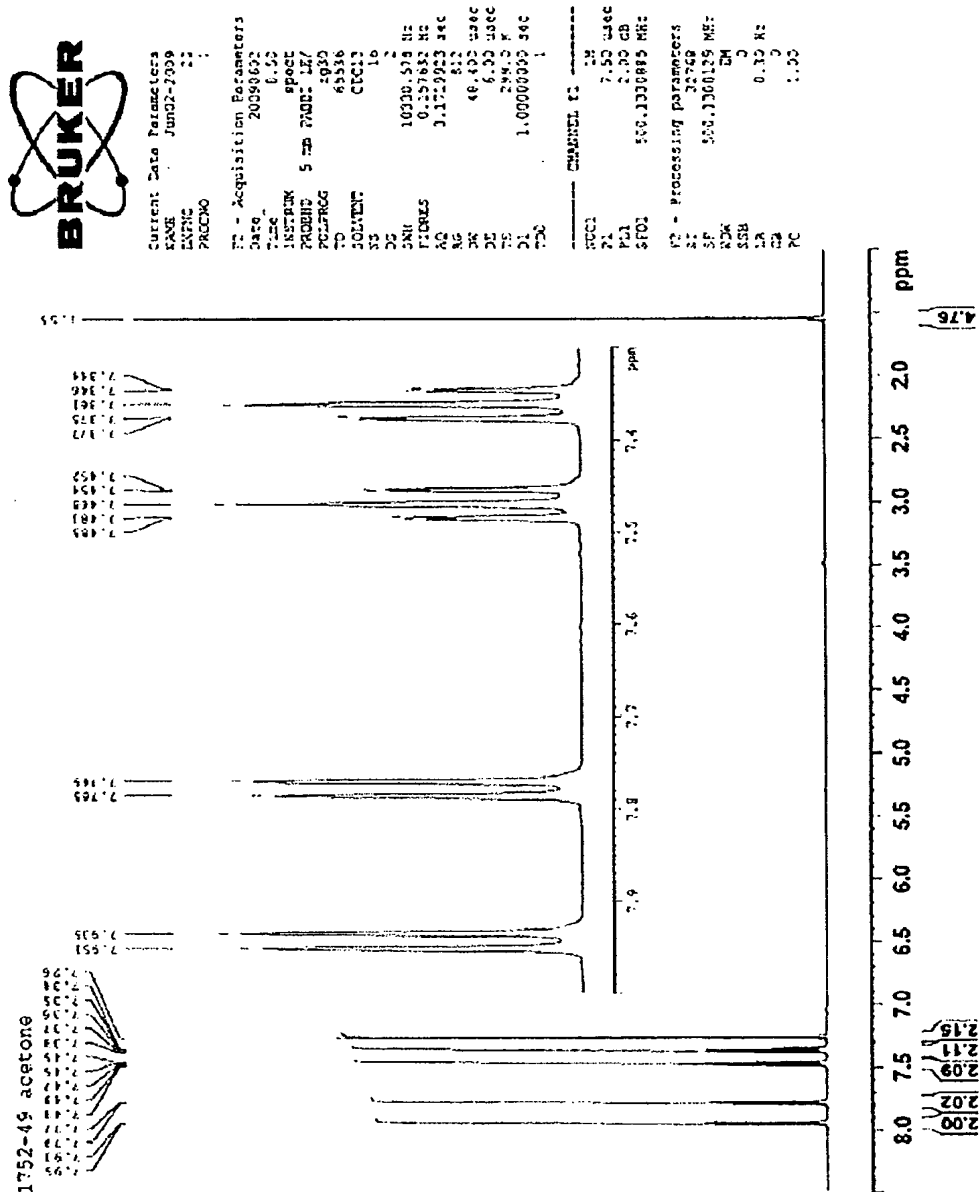


Fig. 2 (Crystal B)



[illegible]

#### Consideration on the results of experiments

Only Crystals A to C were deposited in the experiment process. From the NMR charts shown in Figs. 1 to 3, Crystals A to C were identified as bis(2-benzothiazoyl) disulfide 4, and any peaks attributable to 2 $\beta$ -chloromethyl-2 $\alpha$ -methylpenam-3 $\alpha$ -carboxylic acid benzhydryl ester were not observed. Accordingly, it was confirmed that the crystals deposited during the synthesis of 2 $\beta$ -chloromethyl-2 $\alpha$ -methylpenam-3 $\alpha$ -carboxylic acid benzhydryl ester disclosed in Bull. Chem. Soc. Jpn., 62, 3046-3048 (1989) were by-products, i.e., bis(2-benzothiazoyl) disulfide 4.



6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issued on this application.

Date: Aug. 20, 2009

By: Isao Wada  
Isao WADA